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Chiral polymer catalysts in preparative organic chemistry: a critical overview

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Abstract- Object of the present paper is to provide an up-to-date overview in the field of functional chiral polymers as catalysts in preparative organic chemistry. Attention has been in particular limited to "metal-free" systems, that is, to polymeric systems capable of exerting their own specific catalytic role by virtue of the presence of active groups either directly bound to chiral residues or embedded in a chiral environment. This last can be generated by chiral groups located along or within the polymer backbone, sometimes well far apart from the catalytic sites.For convenience the material has been grouped into two major sections dealing with reactions carried out under homogeneous and heterogeneous conditions, respectively. The first section reports on the activity of different catalysts as tested in the hydrolysis of chiral (optically active or racemic) activated esters, whereas in the second section oxidative, reductive, and nucleophilic additions to prochiral activated carbon-carbon or carbon-oxygen double bond have been reported.

INTRODUCTION

Over the past years a great deal of interest has been focused on organic reactions performed in the presence of functional polymers acting either as reagents or catalysts, as comprehensively outlined in a specific contribution to the present microsymposium (Ref. 1) and in expressely devoted reviews and books (Refs. 2-7). Within this area the polymer matrices can play i) a role of mere support for reactive species and catalytic sites, thus facilitating the work-up of reaction products and allowing for continuous flow processes provided they are insoluble in the reaction medium and specifically shaped in bead form; ii) a direct control of the reaction kinetics as driven by loading and relevant distribution of the active species or catalytic sites along the polymer backbone. These can be placed either within the backbone, or close to it, or spaced apart and can influence the selectivity of the process via intrinsic structural requirements (nature and hydrophilic-hydrophobic balance of the repeating units), macromolecular microtacticity and local or long-range conformational assembling. In preferentially chiral polymer systems this last requirement appears of fundamental relevance to their use in chemical transformations able to discriminate between enantiomeric faces of prochiral substrates or to allow for a "second order kinetic" resolution of racemates.

Within this framework in the present contribution we wish to highlight the results obtained in the use of preferentially chiral polymer systems as "metal-free" polymer catalysts in preparative organic chemistry. For convenience, the contributions provided by other authors and ourselves along that line have been tentatively grouped into two major sections dealing with reactions carried out under homogeneous (polymer catalysts completely soluble in the reaction medium) and heterogeneous conditions (polymer catalysts insoluble in the reaction medium, either monophase or biphase in character) respectively.

Indeed, within the major goal of providing synthetic polymers able to mimick the role of enzymes in bioorganic reactions, the first section is mainly devoted to kinetic studies of esterolysis of activated chiral esters, whereas the second section, aimed to provide synthetic tools of preparative significance, deals with the transformation of prochiral substrates. From a practical standpoint it is fair to mention that the studies reported in both sections do not appear very encouraging indeed, eventhough they offer quite a number of meaningful hints to the basic knowledge of polymer catalysed reactions. More appealing results, from the preparative point of view, are obtained in a series of reactions, included for convenience in the second section, that should be placed however, for their specific features, somewhere in between the two sections. They deal essentially with either oxidative, reductive, or nucleophilic addition to activated prochiral carbon-carbon or carbon-oxygen double bonds.

REACTIONS IN HOMOGENEOUS PHASE

In the last twenty years a wide number of chiral polymers has been synthesized, with functional groups in the side chain able to catalyze organic reactions in homogeneous phase.

To the benefit of a critical survey, they can be substantially confined to two major classes consisting of :

(1) polymers containing the imidazolyl moiety embedded in a chiral environment of different homogeneity
(2) polymers containing oxime or hydroxamic acid moieties placed in different chemical and chiral environments.

By virtue of their own intrinsic structural features those polymer systems have been considered "synthetic enzyme analogs" and the enzyme catalysis elucidation was the major aim of the undertaken investigation specifically focused on the assignment of structure-activity relationship in synthetic synthetic polymer catalysts.

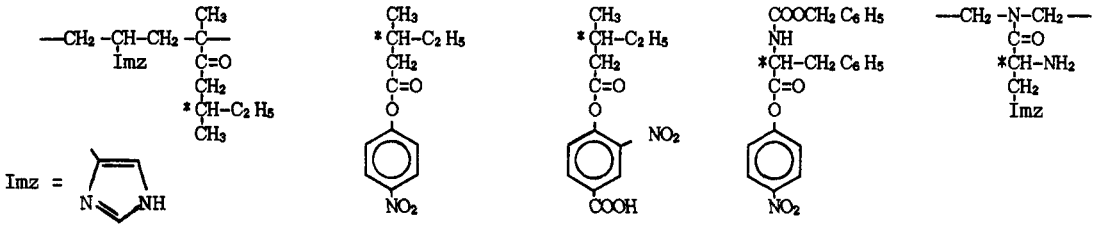
The presence of functional groups such as histidine , and oxime coupled with amine and/or quaternary ammonium group, capable of exploiting esterolytic activity constituted a common feature of the explored polymer systems; hydrolysis of activated esters was taken as a standard reaction.

The prevalent chirality in the systems was either determined by the presence of chiral groups well separated by the active sites or embodied into the structural units bearing catalytically active group. The enantiomeric discrimination efficiency of the different systems was tested in second order kinetic resolution of racemates and/or prevailingly chiral (enantiomer ratio S/R > 1) compounds.

It is fair to remark that beyond the speculative information that have been gained on the specific mechanism of polymer catalysis no example has been so far reported on practical exploitation of the investigated systems in preparative organic chemistry and indeed very slim potential to that purpose can be claimed.

Chiral polymers containing imidazolyl moiety

Overberger and Cho (Ref. 8) have synthesized an optically active copolymer of 4(5)-vinylimidazole and (S)-2,5-dimethyl-1-hepten-3-one (1) by free radical chain copolymerization and investigated its effect on the solvolytic rates , in ethanol-water , of the p-nitrophenyl and 4-carboxy-2-nitrophenyl esters of (R) and (S)-3-methylpentanoic acid (*R*-2, *S*-2 and *R*-3, *S*-3, respectively) and the p-nitrophenyl esters of (R) and (S)-N-carbobenzyloxyphenylalanine (*R*-4, *S*-4). Racemates of 2 and 4 were also tested.



1 2 3 4 5

As reported in Table 1 there are some differences between the solvolytic rates of two enantiomeric substrates but they are well within the range of experimental uncertainty and do not allow to draw conclusions concerning any specific catalytic selectivity by polymer 1.

The pretty high distance of the prevailingly chiral center from the catalytically active imidazole groups was indicated as responsible of the practical lack of enantiomer discrimination.

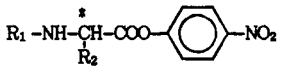
TABLE 1. Apparent first order rate constant for the solvolysis of optically active substrates in the presence of optically active copolymer 1

		k· 10^5 (min^{-1})[a]		
Substrate	pH	(*R*)	(*R,S*)	(*S*)
p-nitrophenyl 3-methylpentanoate (2)	8.0	5.9	6.4	7.2
4-(3-methylpentanoyloxy)-3-nitrobenzoic acid (3)	7.3	18	-	23
	6.3	22	-	23
N-carbobenzoxy-phenylalanine p-nitrophenyl ester (4)	7.2	92	80	78
	8.0	200	180	210

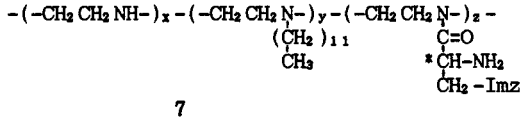
[a] In aqueous ethanol at 26°C, μ = 0.02

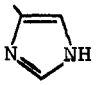
As a further conclusion of the undertaken study the control of higher order structural parameters was proposed as necessary to allow for any valuable enantiomer discrimination. About ten years later Overberger and Dixon (Ref. 9) reported on the preparation of a polymeric

catalyst, substantially different from that previously described (Ref. 8) and obtained simply by grafting L-histidine onto linear polyethylenimine (5) by using dicyclohexyl carbodiimide. By that way approximately one histidine was grafted onto each ethylenimine unit.
In the present case the catalytic site and chiral center were by far much closer than in the previously reported catalyst. The polymer 5 was tested in the solvolysis of the (S)- or (R)-3-methylpentanoate of 2-nitro-4-carboxyphenol (*S*-3 or *R*-3), and in spite of a more direct dissymetric influence on the catalytic site, no enantioselective discrimination was detected.
A few years later Nango et al. (Ref. 10), claimed for a substantial stereoselection in hydrolysis of N-blocked alanine and phenylalanine p-nitrophenyl esters (6) catalyzed by partially alkylated and acylated poly(ethylenimine)s containing covalently bonded L-histidine moiety (7 and 8).
The alkylation with lauryl iodide, either followed or not by acylation of poly(ethyleneimine) was realized in order to generate a mediated hydrophobic environmen around the active catalytic site.



	R_1	R_2
6a	$C_6H_5CH_2$-OOC	CH_3
6b	$C_6H_5CH_2$-OOC	$C_6H_5CH_2$
6c	$(CH_3)_3$C-OOC	$NH_2COCH_2CH_2$



Imz = 

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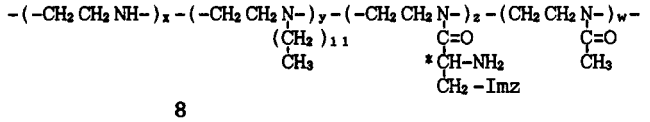

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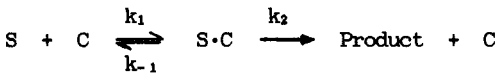
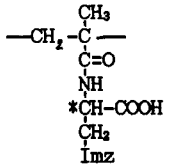
The trend of the release profiles of p-nitrophenolate anion, as followed by UV at pH 7.3 and 25°C, was indicative of a typical stereoselectivity in the rate of comparative hydrolysis for the D and L esters (6a), in the presence of polymer 8.
The analysis of the kinetic data within a Michaelis-Menten approach (Scheme 1) allowed to discriminate between L and D enantiomers of the substrates 6a and 6b with respect to both

Scheme 1 Michaelis-Menten mechanism of hydrolysis:



S = substrate ; C = catalyst
$K_M = (k_{-1} + k_2)/k_1$

k_2 and K_M. In particular for 6b it was observed that D-ester substrate solvolyzed 1.7 times faster than L-ester, and fitted among the other in an enzymatic type catalysis scheme.
In 1982 Cho and Shin (Ref. 11a) prepared imidazole containing polymers starting from N-methacryloyl-L-histidine (9) and N-methacryloyl-L-histidine methyl ester (10) that were free radically homopolymerized or copolymerized with dodecyl methacrylate to provide systems with a modulated hydrophobic character.



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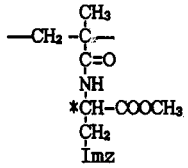

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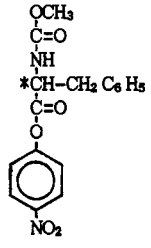

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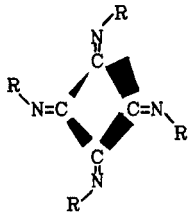
Their catalytic activity was tested in the solvolysis of the p-nitrophenyl esters of N-methoxycarbonyl-D- and L-phenylalanine (D-11 and L-11). The 9 and 10 homopolymers did not exhibit any catalytic stereoselectivity whereas for the corresponding hydrophobic copolymers

with dodecyl methacrylate a noticeable steroselectivity was detected. A further indication was therefore gained that hydrophobic interactions are certainly playing a key role in affecting the stereoselective pathway of the catalysis by "polymeric imidazoles".
The role of hydrophobic interactions in the enantioselective hydrolysis was further explored by the same authors (Ref. 11b). By using the same polymer catalyst, a more hydrophobic substrate such as p-nitrophenyl esters of D- (or L-) N-benzyloxycarbonylphenylalanine (**4**) was tested under different temperature and solvent conditions.
In agreement with what previously observed, polymers **9** and **10** did not provide any better improvement in enantioselectivity discrimination whereas the corresponding more hydrophobic dodecyl methacrylate containing copolymers ,not only were characterized by an enhanced catalytic activity but also increased the degree of enantioselectivity with preference for the L-enantiomer. A k_L/k_D = 1.5 ÷ 1.7 was evaluated.
It is also worth underlining that the reaction rate abnormally increased with decreasing temperature, thus substantiating that hydrophobic interactions are operative in the rate determining complex formation step. Analogous results in stereoselectivity were reached at a 20% water content in the aqueous-ethanol solvent medium, where maximization of the hydrophobic interactions occurs, as also confirmed by recent data obtained by using copolymers containing ionic surfactant counits that seem to help to increase the reaction rate without depressing the enantioselectivity (Ref. 12). More recently poly(isocyanide)s based on dipeptides and tripeptides containing a L-histidyl residue (**12**) have been prepared. They are known to adopt a stable helical structure (Ref. 13), in which their side chains are arranged in stacks enclosing four grooves running parallel to the polymer axis thus providing a chiral surface that should be in principle suitable for chiral recognition.
Indeed the results obtained in the chromatographic separation of enantiomers and diastereoisomers with conformationally stable poly(trityl methacrylate) type polymers (Ref. 14) appear rather encouraging in promoting research in the field of catalytic reactions in which a stereochemical recognition could be achieved on catalytic sites located on portions of conformationally homogeneous extended helices.



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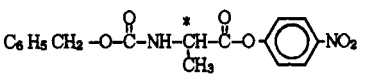
R ◻ Ala/His
Ala/Ser
Ala/His/Ser

Interestingly, the prepared polymers are soluble in water and maintain a prevalent helicity even in solution. Rate constants were measured for the hydrolysis of p-nitrophenyl and dinitrophenyl esters catalyzed by imidazolyl-containing polymers and copolymers of isocyanides.
The catalytic rate constants, k_a, in the hydrolysis of chiral amino acid 4-nitrophenyl esters by the above systems were very low and related to the high pKa values of the imidazolyl functions. They were in any case more active than the corresponding low molar mass analogs as a consequence of cooperative effects established in the polymers by the imidazolyl-imidazolyl or imidazolyl-carboxylate neighbouring interactions.Significant differences in activity with respect to L- and D-esters could not be observed. However, in the presence of cationic surfactants able to generate a pseudo-hydrophobic phase around negatively charged polymer molecules , activities were much higher and enantioselectivities falling outside the insignificant range ($k_L/k_D \approx 0.9$-1.1) were clearly observed in a number of cases. The latter observation is worth of interest because the surfactant itself is achiral and the anticipated use of a proper surfactant should help to improve the enantioselectivity degree by virtue of additional discriminating effects related to the generation of a chiral pseudophase around the catalytic sites.
The development of the research in the solvolysis of activated esters by chiral polymers containing imidazolyl groups appears nowadays oriented towards more complicated systems, that cannot be easily rationalized and pose themselves something in between homogeneous and micellar catalysis.
Recently Japanese researchers (Refs. 15 and 21) have studied the stereoselective hydrolysis of enantiomeric esters catalyzed by N-decanoyl-histidine or dipeptide derivatives containing a histidyl residue in the presence of poly(ethylenimine) derivatives. These catalytic systems are substantially different from that, above described, in which L-histidine residue is covalently bound to poly(ethylenimine) (Ref. 3)
In Scheme 2 the structures of the substrates (**13** and **14**) and catalysts (**15-17**) used by Ihara et al. (Ref. 15) are reported.

Scheme 2 Structures of substrates and catalysts investigated by Ihara et al. (Ref. 15):

Substrates



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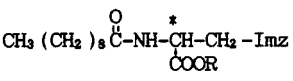
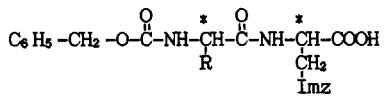
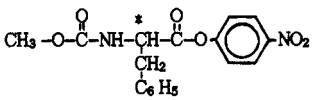
Catalysts



15 R = H , CH_3



16 R = $CH_2CH(CH_3)_2$, $CH_2C_6H_5$



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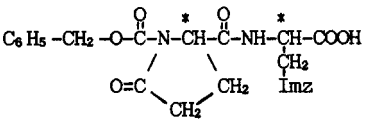

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Hydrolysis reaction rates were followed by UV measurements at pH 7.3 and 25°C. In particular a control was performed of the variation of the pseudo-first order rate constant (k_{obs}) and stereoselective ratio (L/D) for solvolysis of chiral substrates as function of concentration of L-histidine derivative in the presence of polyethylenimine modified with lauryl bromide (Ref. 10) and by partial quaternization with dimethyl sulphate.

All the catalysts containing L-histidine residues stereoselectively hydrolyze the L-enantiomer of the substrates. This preference indicates that the stereoselective control is mainly determined by acyl transfer to the imidazole function at the active site of the optically active catalysts in polymer domains.

Most likely, due to apolar interactions or hydrogen bonding formation, the amino acid residues next to the imidazoles contribute to an increase in the stereoselectivity. In addition, stereoselectivity depends on the structure of the substrate: the stereoselectivity ratios for **14** were greater than those observed for **13** in all the examined cases.

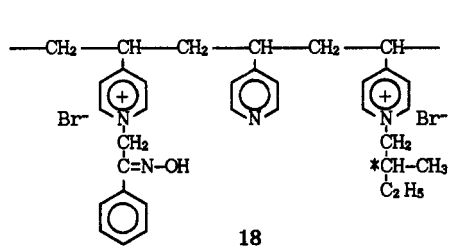
It is finally interesting to stress that the stereoselectivity for **13**, which is an isomer of **14**, does not show any special dependence on the structure of the catalyst tested in the presence of polymer, all the values of stereoselectivity being included in the 1.3-2.3 range. In contrast, stereoselective preference for **14** largely depends on the structure of the catalyst. This behaviour has been taken as an indication of the importance of specific interactions of the active imidazole groups with the substrate in the polymer domains.

In particular the study of the viscosity behaviour of quaternized polyethylenimines (Ref. 16), that appears similar to that of linear flexible polyelectrolytes, indicates that these polymers swell in dilute salt solution. This swelling effect can also be evidenced by the dependence of the rate constants on catalyst concentration in the hydrolysis of chiral nitrophenyl esters.

Stereoselective preference was exhibited in hydrolyses catalyzed by the quaternized polymers containing covalently bound L-histidine moieties. Maximum stereoselectivity was manifested at polymer concentration corresponding to nonswollen conformational states. As previously anticipated on the possible role exerted by added surfactants, the addition of cetyltributylammonium bromide to the lauryl-L-histidine/polyethyleneimine system leads to the preferential hydrolysis of the L-ester whereas in the absence of the surfactant the D-enantiomer is preferentially consumed (Ref. 10).

Chiral polymers containing oxime or hydroxamic residues

Within this line some contributions were provided by two of us in cooperation with others and we shall report herewith on the major results obtained. The systems that have been studied are in all cases multifunctional, and in addition to the oxime moiety they also contained units with amino and quaternary ammonium group (Refs. 17 and 18). A first example consisted of poly(4-vinylpyridine) modified by partial quaternization with phenacyloxime bromide and with (+)(S)-1-bromo-2-methylbutane to obtain a water soluble terpolymer (**18**).



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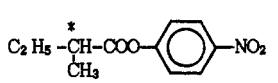

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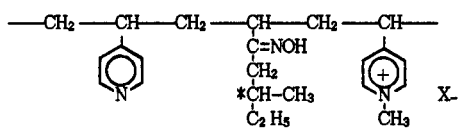
The terpolymer **18** was used as a catalyst in the esterolysis of optically active and racemic p-nitrophenyl 2-methylbutanoate (*S*-**19** and *R,S*-**19**) at pH 8.50 and 26°C.
At first, a rapid evolution of the reaction product (p-nitrophenolate ion) is observed, followed by a decrease of reaction rate up to a stationary state where the reaction rate is constant. That behaviour has been explained assuming that the first step corresponds to the nucleophilic attack of the oxime anion on the substrate while the second corresponds to the hydrolysis of the N-acylated derivative, giving rise to the regeneration of the catalytically active species. Both *S*-**19** and *R,S*-**19** are hydrolyzed at the same overall rate.
The lack of chiral discrimination substantially agrees with the mechanistic picture of the reaction, in which the substrate interacts with the oxime anion during the first reaction step and in the second most likely interacts with 4-vinylpyridine groups that assist the deacylation step.
The optically active groups, carrying the same positive charge as the oxime-containing units, undergo electrostatic repulsion and are not probably involved in the acylation step.
A moderate discrimination of the antipodes of p-nitrophenyl 2-methylbutanoate (**19**) is observed with the catalyst obtained from the copolymer of 4-vinylpyridine with (+)(S)-5-methyl-1-hepten-3-one by reaction with hydroxylamine (**20**).



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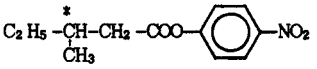

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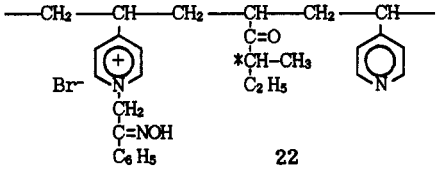
The same catalyst hydrolyzes at comparable rate the two antipodes of p-nitrophenyl 3-methyl pentanoate (**21**) due to the lack of any steric control and as a consequence of the larger distance of the chiral center from the ester group with respect to the inferior homologue.
The low chiral discrimination observed for catalyst **20** was explained considering the high value of pK_a (11.4) for the oxime groups, which forced to work at a pH of 10.0 where the buffer reaches a ground activity in esterolysis comparable with that of polymer catalyst thus preventing the reaction from reaching a stereoselectivity maximum.
Analogous unsatisfactory results were also obtained in the solvolysis of **19** by means of the terpolymer **22**, prepared by partial quaternization with phenacylbromide oxime of the pyridine groups of a copolymer of 4-vinylpyridine with (+)(S)-4-methyl-1-hexen-3-one (Ref. 18).



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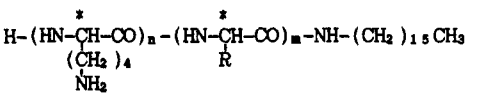
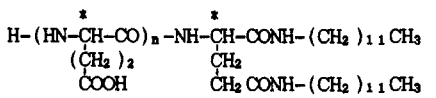
The results so far obtained appear to fit in the general approach by Harun and Williams (Ref. 19) according to which linear systems do not yield satisfactory enantioselective discrimination. As a consequence they studied the possibility of incorporating an optically active monomer into a microgel capable of forcing the substrates to take pathways discriminating on enantioselectivity grounds.
Accordingly, spherical particles of diameter between 20 and 200 nm composed of crosslinked polymeric chains were prepared. These particles could be dispersed in water provided they possessed groups with sufficient hydrophilic character and the resulting colloidal suspension was considered by the authors as a polymer solution.
A mixture of (-)-menthyl acrylate (30 mol %), 2-hydroxyethyl methacrylate (25 mol %), 1,2-ethylene dimethacrylate (2 mol %), acrylic acid (15 mol %) and O-benzoyl-N-methacryloyl-hydroxylamine (28 mol %) was polymerized under emulsion conditions and polymer was oximated by polymer-analog reaction procedure to give microgel type polymers.
The solvolysis of chiral p-nitrophenyl esters by that microgel led to saturation phenomena in the kinetic profiles consistent with the formation of a complex followed by reaction of the ester in the complex species. The polymer discriminates between R- and S-forms of a chiral substrate in both complexing and catalytic steps.
The data are claimed consistent with the existence of chiral spaces in the microgel beads specifically shaped to accept the chiral substrate through discriminating pathways. Indeed, even though the reported systems are very suggestive and promising, further data on the micromorphology of the microgel beads are needed before drawing any significant conclusion.
More interesting systems, better classified as of "micellar type" are those recently investigated (Ref. 21) in view of establishing the structure of chiral aggregates of amphiphiles with polypeptide-head groups (**23a-d**)



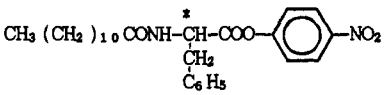
R

23a	$(CH_2)_4NH_2$	(m + n = 3,8,13 and 18)
23b	CH_3	(m = 1 , n = 10)
23c	$CH_2C_6H_5$	(m = 1 , n = 12)
23d	$CH_2CH(CH_3)_2$	(m = 9 , n = 9)



24

The **23a-d** polymeric compounds generate micelles with structural asymmetries related to the presence of peptide head-groups in α-helix or pleated ß-sheet conformation. Compound **24** gives also helical superstructures composed of single-walled bilayer membranes.
The effects of chiral matrix micelles on cleavage reactions of the chiral ester **25** by using achiral hydroxamic acids **26-28** were investigated and evidences for a micellar type catalysis have been presented.



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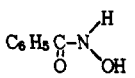

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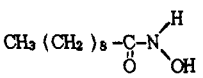

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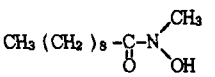


28

In the absence of **27** no enantioselectivity was observed regardless of conformational change of micellar matrix (L/D=1) and the chirality of matrix seems to play no role. On the contrary, some selectivity was induced by the addition of hydroxamic acid **27**. Since **27** is achiral and no enantioselectivity is expected to take place, the observed selectivity can be claimed to arise from cooperative effects between the chiral micelles and achiral nucleophiles.
It could be supposed that the secondary structure asymmetry introduced by poly-L-lysine is important for enantioselectivity. The selectivity for L- and D-enantiomers was influenced by the addition of $NaClO_4$ or poly(acrylic acid).
For example, the value of k_L/k_D changed from 2.4 to 0.7 in the case of amphiphile **23a**, and the selectivity change is related to the conformational change from a random coil to α-helix upon the addition of $NaClO_4$.
The selectivity also increased with the degree of polymerization of polypeptide head-groups of the matrix amphiphiles. The enantioselectivity changed by effect of structural differences of added hydroxamates and was also sensitive to structural differences of the peptide moiety in matrix amphiphiles.
For instance when a spacer such as L-phenylalanine or L-alanine was introduced between the long-chain alkyl group and poly-L-lysine-head group, the ratio of k_L/k_D increased from 2.1 to 3.2 under conditions favouring the random coil and changed from D-selectivity (k_L/k_D=0.7) to L-selectivity (k_L/k_D=2.0) when conditions for an α-helix conformation were established.

REACTIONS IN HETEROGENEOUS PHASE

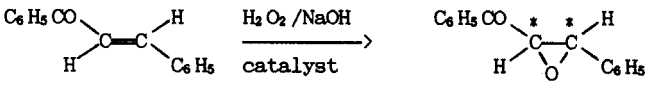
As anticipated, the present section includes a variety of reactions that have been mainly carried out under heterogeneous conditions in aqueous/organic medium and in the presence of crosslinked polymers.
The investigated polymers are characterized by the presence of prevailingly chiral groups either in the polymer main chain or in the side chain and accordingly they have been treated in two separate sections.
Prochiral carbonyl compounds, activated olefins, and compounds containing activated methylene groups are the substrates that have been submitted to reduction, carbenation, alkylation, esterification, epoxidation, and nucleophilic addition.
For convenience the different reactions are examined in specific subsections.

Polymers with chirality in the main chain

Oxidation reactions

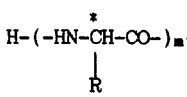
The investigated asymmetric oxidation reactions are almost exclusively limited to the epoxidation of activated prochiral double bonds, by using conventional epoxidation agents in the presence of optically active polymers (Scheme 3).

Scheme 3 Epoxidation of chalcone by the H_2O_2/NaOH system:



29

Epoxidation of chalcone (**29**) and related compounds has been carried out under triphase conditions in the presence of different synthetic polypeptides (**30–40**) terminated by an amino or an ammonium group (Refs. 22 and 23).



	R	R'
30	CH_3	$-NHC_4H_9$
31	*i*-C_3H_7	"
32	*i*-C_4H_9	"
33	*s*-C_4H_9	"
34	$CH_2C_6H_5$	"
35	$CH_2COOCH_2C_6H_5$	"
36	$CH_2CH_2COOCH_2C_6H_5$	"
37	CH_3	$-NH(CH_2)_2N(C_2H_5)_2$
38	CH_3	$-NH(CH_2)_2\overset{+}{N}(C_2H_5)_3\ Br^-$

39	$[Leu/Ala]_{10}$	molar ratio Leu/Ala = 1
40a	$[Val/Ala]_{10}$	" Val/Ala = 1
40b	"	" Val/Ala = 7/3
40c	"	" Val/Ala = 9

Epoxidation of chalcone in the triphase system water/toluene/poly-(S)-alanine occurs with good chemical yields and high asymmetric inductions. Both chemical and optical yields increase with increasing the degree of polymerization of the catalyst, whereas in the absence of the polypeptide no reaction occurs (Table 2). The presence of a terminal tertiary amine or quaternary ammonium group not only reduces the chemical yield, but also negatively affects the asymmetric induction. No direct correlation is found between the dielectric constant of the solvent and enantioselectivity (Table 3).

TABLE 2. Epoxidation of chalcone with H_2O_2 in toluene in the presence of different catalysts

Catalyst type	m	Yield (%)	E.e. (%)
none	-	0	0
30	5	9	11
30	7	18	28
30	10	78	83
30	30	57	93
37	10	52	15
38	10	62	20

TABLE 3. Epoxidation of chalcone with H_2O_2 in different solvents in the presence of catalyst **30** (m ≅ 10)

Solvent	Time (hr)	Yield (%)	E.e. (%)
None	24	100	0
Toluene	24	77	83
CCl_4	28	75	88
Chlorobenzene	48	83	84
CH_2Cl_2	50	78	74
Cyclohexane	48	92	48
Hexane	24	95	14

Comparison of the results obtained in the presence of different poly(α-aminoacid)s indicates that both chemical and optical yields heavily depend on the structure of the repeating units (Table 4). It is worth noting that racemic polyalanine exhibits a much lower activity than the corresponding optically active polypeptide.

These results seem to indicate that the enantioselectivity is closely related to the α-helical content of the polypeptide. Accordingly, when the reaction is carried out in the presence of random copolymers of L-alanine with L-valine, both the chemical and the optical yields decrease on increasing the content of (L)-valine units, whose preferred conformation is the β-pleated sheet. However this explanation does not account for the large optical yield obtained in the presence of poly(L-isoleucine) (**33**) that has a β-structure, and the low asymmetric induction of poly(benzyl L-aspartate) (**35**) and poly(benzyl L-glutamate) (**36**) that have both an α-helical structure. Moreover the levorotatory epoxychalcone enantiomer is formedin the presence of both catalysts **35** and **36**, that adopt α-helical conformations chracterized by opposite handedness. It is possible that the asymmetric

TABLE 4. Epoxidation of chalcone with H_2O_2 in the presence of catalysts 30–40.

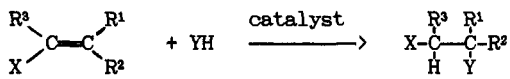
Catalyst type	m	Time (hr)	Yield (%)	E.e. (%)
30	10	28	75	93
30 rac.	10	24	5	0
30	30	28	77	96
31	10	168	5	10
31	30	144	4	33
32	10	28	60	84
32	30	28	44	88
33	10	72	76	95
34	10	72	32	1
35	10	456	8	3
36	10	144	12	12
39	10	24	67	95
40a	10	96	39	88
40b	10	192	14	39
40c	10	168	9	17

induction in the epoxidation is governed by the local ordering of the polypeptide matrix, as observed in the asymmetric synthesis performed in the presence of cholesteric liquid crystals (Ref. 24).
The oxidation of sulphides, carried out under biphase conditions in the presence of a natural polypeptide (bovine serum albumine), gives the corresponding S-oxides having optical purity between 2 and 64%, depending upon the structure of the substrate, catalyst concentration, and reaction time (Refs. 25 and 26).

Michael type addition

The reaction that consists in the addition of active hydrogen compounds to activated double bonds, as represented in Scheme 4, can lead to one or two new asymmetric carbon atoms in the relevant reaction product.

Scheme 4 Michael type addition:



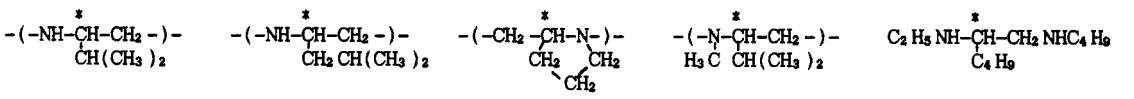
X = activating group Y = nucleophilic group

The activity of poly(benzyl L-aspartate) (35), poly(benzyl L-glutamate) (36), and poly(L-alanine) (30) has been investigated in the addition of dodecanethiol to isopropenyl methyl ketone (Refs.27-32). The reported data (Table 5) indicate that in the case of catalysts 35 and 36 the reaction rate generally decreases while increasing the degree of polymerization, whereas it is fairly independent of molecular weight in the case of catalyst 30. The ratio weight of catalyst/mmol of substrate and the molar ratio catalyst/substrate were kept constant in the former and in the latter case, respectively, thus indicating that the catalytic activity arises only from the terminal amino group. Even though polypeptides 35 and 36 are known to assume helical conformations of opposite handedness, the addition products obtained in the presence of 35 have optical rotation of the same sign, but lower in magnitude than the

TABLE 5. Addition of dodecanethiol to isopropenyl methyl ketone carried out in chloroform in the presence of synthetic polypeptides.

Catalyst Type	m	Time (days)	Conv. (%)	$[\alpha]_D^{25}$	Catalyst Type	m	Time (days)	Conv. (%)	$[\alpha]_D^{25}$
none	-	35	0	-	35	5	26	91	-0.35
						10	40	76	-0.48
30	3	66	88	-2.00		20	34	64	-0.24
	5	41	64	-1.28					
	8	27	65	-0.91	36	6	26	66	-0.32
	10	41	67	-0.84		10	37	68	-2.50
	12	31	58	-0.66		12	44	50	-0.36
	20	58	72	-0.74		20	48	74	-0.32

products obtained by catalyst **36**. This fact suggests that the absolute configuration of the predominant antipode in the product is mainly determined by the chirality of the terminal unit and to a lesser extent by the handedness of main chain conformation (Refs. 27 and 28). In the case of catalyst **30**, the observed asymmetric induction monotonically decreases on increasing the degree of polymerization. Catalyst **30** has been shown to have a ß-conformation when m = 3 whereas it may assume an α-helical conformation at higher DP_n. It seems therefore that in this case the main chain α-helix does not contribute to the asymmetric induction, most likely due to its compactness (Refs. 29 and 31). The activity of **30** has also been investigated in base-promoted reactions such as dehydro-halogenation of halohydrins, the Darzens condensation of phenacyl chloride with benzaldehyde, and the addition of ethyl nitroacetate to chalcone (Ref. 22). In all cases barely detectable asymmetric inductions have been observed. Polymeric amines **41-44** have been used as catalysts in the addition of methanol and dodecane-thiol to α,ß-unsatured ketones and esters (Refs. 33-37). In all cases the reaction products resulted optically active, but the optical yield was limited at most to a few percent.



41 **42** **43** **44** **45**

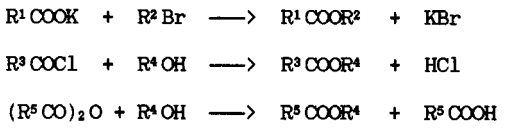
The polymeric catalysts exhibit a larger asymmetric induction than the corresponding low molecular weight structural analog **45** (Table 6), and a polymer effect can be claimed in improving the optical yield in asymmetric induction.

TABLE 6. Addition of dodecanethiol to racemic α,ß-unsaturated compounds carried out in the presence of polymeric catalyst **43** and its low molecular weight analog **45**.

Substrate	$[\alpha]_D^{25}$ **43**	**45**
Methyl methacrylate	+1.20	+0.14
Methyl crotonate	+0.19	0
Methacrylonitrile	+0.08	0
Methyl isopropenyl ketone	+0.37	-0.16

Synthesis of esters

Optically active polymeric amines **41** and **44** have been used as catalysts (Refs. 38-40) in esterification reactions based on conventional routes of esterification of anhydrides and acid chlorides with alcohols or alkylation of potassium salts with alkyl bromides:



The data reported in Table 7 indicate that small but definite optical yields are obtained in most cases, even though these cannot be claimed of any practical meaning in preparative organic synthesis.

TABLE 7. Esterification reactions carried out in the presence of optically active polymeric amines.

Catalyst	Acyl compound	Alkyl compound	Conv. (%)	E.e. (%)
44	$R^1 = CH_3$	$R^2 = s\text{-}C_4H_9$	38	2.4
	CH_3	α-phenylethyl	45	1.5
	C_2H_5	$s\text{-}C_4H_9$	44	4.2
	$s\text{-}C_4H_9$	$n\text{-}C_4H_9$	41	2.5
	$R^3 = CH_3$	$R^4 = s\text{-}C_4H_9$	96	1.1
	$s\text{-}C_4H_9$	C_2H_5	75	0
	$R^5 = s\text{-}C_4H_9$	C_2H_5	70	0
41	$R^1 = s\text{-}C_4H_9$	$R^2 = n\text{-}C_4H_9$	36	2.5

Esterolysis reactions that are normally performed in aqueous/ethanol solvent have constituted the major object of the previous section and are not further considered.

Polymer catalysts with chiralty in the side chain

Within this general class of polymeric catalysts, for homogeneity convenience we may distinguish between systems in which the chiral groups are directly bound to the active centers and systems in which the catalytic sites are far apart from the chiral group.

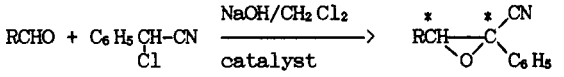
Chiral groups directly bound to the active centers

Polymer catalysts belonging to this group have been used in epoxidation reactions, Michael type additions, and more generally in phase transfer reactions.

Epoxidation reactions

By using polymeric onium salts, chiral epoxides have been prepared by oxidation of olefinic substrates (Refs. 41 and 42) or carbenation of carbonyl compounds (Ref. 43). In the former case quininium salts, either directly bound or spaced apart from 2%-DVB crosslinked polystyrene, and a copolymer acrylamide/quinine have been used. Enantiomeric excesses lower than 10% have been obtained in the epoxidation of chalcones. Rather surprisingly the above polymeric systems exhibit an enantiomeric discrimination one order of magnitude lower than the corresponding low molecular weight analogs (Ref. 44), accordingly the spaced system displays a larger discrimination efficiency. An analogous trend is observed in the Darzens reaction between acetaldehyde or benzaldehyde and 1-chloro-1-phenylacetonitrile (Ref. 43) catalyzed by ephedrinium salts supported on 2%-DVB crosslinked polystyrene.

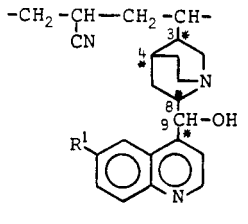
Darzens condensation reaction



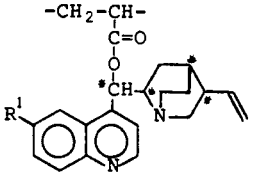
Higher discrimination efficiency are observed in the reaction of carbonyl compounds with chloromethyl-*p*-tolylsulphone carried out in the presence of the same catalyst (Ref. 43).

Michael type additions

The polymeric catalysts used can be divided into two main classes: polymeric alkaloids and polymer bound chiral amine derivatives, even if it is fair to mention that the first known asymmetric Michael addition was carried out in the presence of optically active natural quartz (Ref. 45). In the first class of catalysts there are copolymers of cinchona alkaloids with acrylonitrile (**46a-46d**, Refs. 41 and 46-51), homo and copolymers of O-acryloylquinine (**47a** and **47b**, Refs. 52-55)

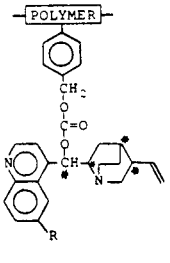


		R^1	C_3	C_4	C_8	C_9
46a	Quinine	OMe	R	S	S	R
46b	Quinidine	OMe	R	S	R	S
46c	Cinchonidine	H	R	S	S	R
46d	Cinchonine	H	R	S	R	S



	R^1	C_4	C_8	C_9
47a	OMe	S	S	R
47b	H	S	R	S

and cinchona alkaloids bound to crosslinked polystyrene (**48-50**, Refs. 42 and 56-60).



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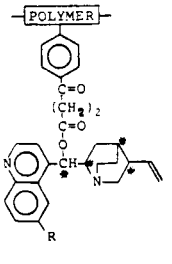

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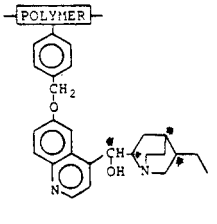

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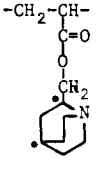
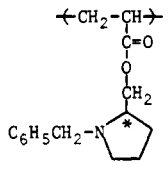


51

To the second class belong polymers such as poly(2-quinuclidinylmethyl acrylate) (**51**, Ref. 55), poly(N-benzyl-2-pyrrolidinylmethyl acrylate) (**52**, Ref. 54) and polystyrene bound onium salts derived from L-methionine (**53** and **54**, Refs. 56 and 61) and (-)-ephedrine (**55**, Ref. 56).



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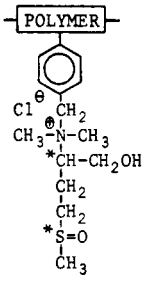

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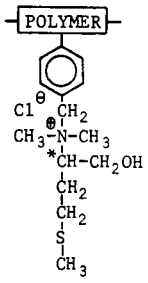

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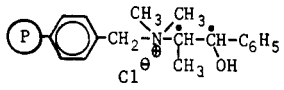
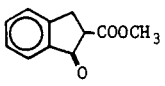
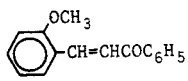


55

The addition of active hydrogen compounds (alcohols, thiols, ß-ketoesters, and nitroalkanes) to activated double bonds performed in the presence of **46-50** catalysts occurs with a maximum enantiomeric excess of about 60%. The stereochemistry of the addition products is determined mainly by the C_3 absolute configuration, whereas in the case of low molecular weight model compound the control is generally played by the C_8 and C_9 absolute configurations (Refs. 47-51), thus indicating the key role of the macromolecular structure. No apparent difference was detectable in the results obtained in Michael reactions carried out in the presence of **47a** and **51**, indicating that the quinoline moiety is not essential for the reaction stereochemistry (Ref. 55). On the contrary the presence of both a free hydroxyl group and a tertiary amine is vital for the stereochemical control of the addition step (Refs. 41 and 46-48).
Some of the results obtained in Michael addition reactions carried out in the presence of catalysts **46-55** are summarized in Table 8.

TABLE 8. Michael type addition reactions carried out in the presence of polymer catalysts containing optically active groups directly bound to the active centers.

Catalyst	Reagents		Product		Ref.
	Active hydrogen compound	Activated double bond compound	$[\alpha]_D^{25}$	E.e. (%)	
47a	CH_3OH	$CH_3-\underset{C_6H_5}{C}=C=O$	-16.2	15	52
47b			+38.1	35	52
52			- 5.5	5	54
51			-10.0	9	55
46a			-24.1	30	51
46b			+33.7	42	51
48			- 6.5	8	60
49			- 8.5	11	60
50			- 1.9	2	60
53			0	0	61
55			0	0	56
46a	$C_6H_5CH_2SH$	$C_6H_5CH=CHNO_2$	+18.7	9	41,48,51
46b			+36.3	18	41,48,51
46c			+25.7	13	41,48
46d			+25.1	12	41,48
53	$C_6H_5CH_2SH$		0	0	61
46a	$C_{12}H_{25}SH$	$CH_2=\underset{CH_3}{C}-COCH_3$	- 7.9	45	41,50
46b			- 9.9	57	41,50
46c			- 6.6	38	41,50
46d			+ 8.2	47	41,50
46a	$C_{12}H_{25}SH$		+16.0	20	47
46b			+ 6.1	8	47
46c			+ 2.9	4	47
46d			+ 9.3	12	47

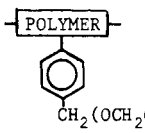
Phase transfer reactions
In previous subsections, some of the reactions quoted have been carried out under conditions in which a phase transfer process was implied. Indeed in the present subsection we have collected most of the other reactions that are known to be run in aqueous/organic medium, in

the presence of insoluble polymeric ammonium or phosphonium salts.
The $NaBH_4$ reduction of a series of aryl alkyl ketones, carried out under phase transfer conditions in the presence of quaternary onium salts (derived from chiral amines such as ephedrine, brucine, and cinchona alkaloids) supported on crosslinked polystyrene, has been rather extensively investigated (Refs. 58 and 59). Data reported in Table 9 indicate that an asymmetric induction is observed only when both the substituents flanking the carbonyl group are bulky enough to allow a sufficient stereochemical discrimination. Moreover, as in the case of Michael addition, the absence of a hydroxyl group in β-position to the onium group depresses the optical purity of the reduction products (Ref. 58). A limited influence on the extent of asymmetric induction exerted by the degree of crosslinking, polarity of the reaction solvent, and experimental conditions has been also observed (Refs. 58 and 59).

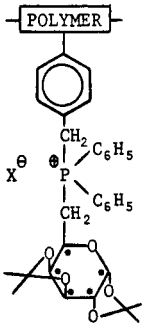
TABLE 9. Reduction of phenyl ketones carried out in the presence of chiral ammonium salts supported on crosslinked polystyrene.

Onium salt derived from	Ketone	$[\alpha]_D^{25}$	E.e. (%)
Quinine	*p*-bromoacetophenone	0	0
"	*p*-methoxyacetophenone	0	0
"	*p*-nitroacetophenone	0	0
"	acetophenone	0	0
"	propiophenone	0	0
"	butyrophenone	+2.1	5.1
"	pivalophenone	+2.9	12.8
Cinchonidine	pivalophenone	+3.0	13.1
Cinchonine	"	-3.1	13.7
Ephedrine	"	+3.4	14.8
Brucine	"	0	0

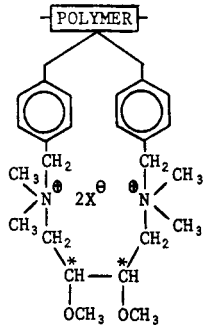
Sherrington and coworkers (Refs. 62-64) have reported the synthesis of the rather complex polymer supported optically active catalysts **56-59**.



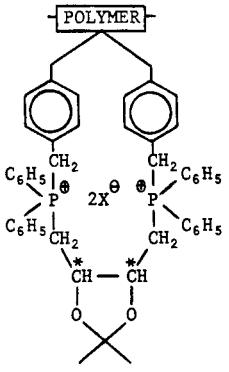
R* derived from
56a L-prolinol
56b L-proline
56c 5-hydroxy-L-proline
56d (-)-menthol
56e (-)-borneol



57



58



59

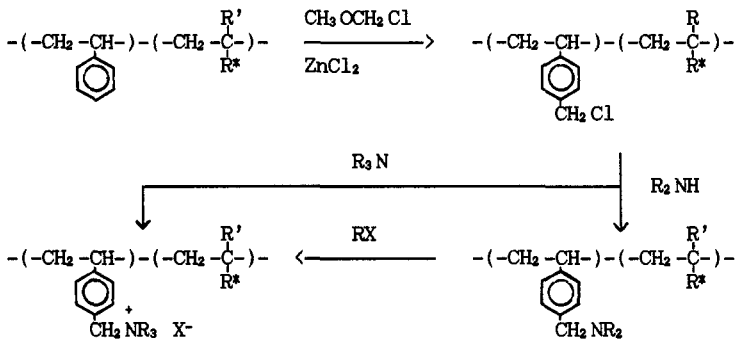
The activity of these polymeric catalysts has been investigated in a series of reactions such as Michael addition, epoxidation of chalcones, $NaBH_4$ reduction of ketones, and displacement reactions of racemic bromides by sodium phenoxide or sodium azide (Ref. 65). Most of the catalysts provided fast reactions and good chemical yields,however in no case significant enantiomeric excesses were achieved. Analogously in the alkylation of phenylacetonitrile, carried out in the presence of polymer supported (-)-menthylamine (Ref. 71), and in the partial acetylation of 1-phenylethanol carried out in the presence of catalysts **47a**, **52**, and **55** (Ref. 53), the reported asymmetric induction is very low, if any.Very low optical yields and extensive catalyst decomposition were observed also in the alkylation of phenylacetonitrile catalyzed by poly(4-vinylpyridine) partially quaternized with (S)-2-methylbutyl groups (Ref. 66).

Catalysts with the active sites far apart from the chiral centers

Very often, under the adopted reaction conditions, even polymer supported onium salts may suffer the Hofmann decomposition reaction that gives rise to a loss of specific activity that in the case of catalysts with active sites directly bound to chiral groups is accompained by an undesiderable drop of chirality. The possible formation of significant amounts of optically active decomposition products, not easily separable from the reaction products, leads to a lack of reliability on the stereoselectivity of the investigated catalysts (Ref. 67).
Systems able to overcome these drawbacks are in our opinion those having chiral groups assembled in a chemically and stereochemically stable macromolecular backbone. In this respect

copolymers of optically active monomers with vinylaromatic comonomers, for which it has been proved that the aromatic units are inserted in a highly dissymmetric environment (Refs. 68 and 69), appear to be well suited. Introduction of the active groups at the level of the aromatic moiety, via conventional synthetic routes (Scheme 5), occurs without any appreciable variation of both main chain and side chains stereochemistry (Ref. 70). By following this route and starting from suitable comonomer mixtures, it has been possible to prepare a large series of polymeric quaternary ammonium salts characterized by different amphiphilic properties, depending on the structure of the chiral comonomer, chemical composition, distribution of monomer units and degree of functionalization of the aromatic nuclei (Refs. 70-76).

Scheme 5 Polymeric onium salts by chemical transformation of preformed polymers:

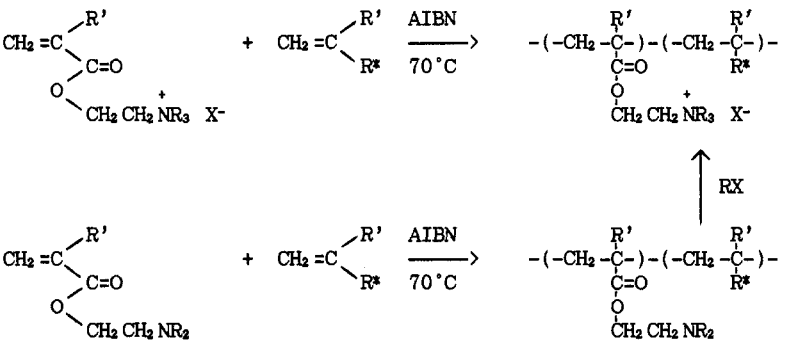


R' = H, CH_3 R* = -COOMenthyl*

R' ◻ H R* = $-CH_2\overset{*}{C}H(CH_3)C_2H_5$, $-\overset{*}{C}H(CH_3)CH_2CH_2CH_2(CH_3)_2$

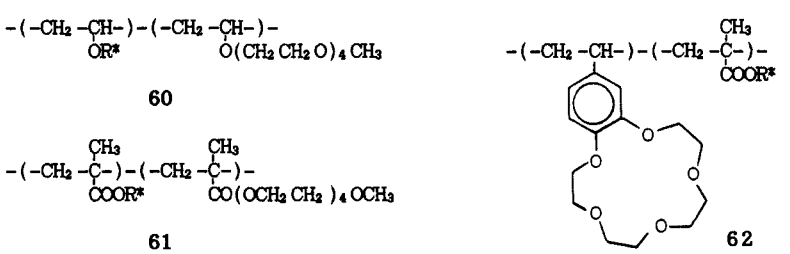
Alternatively, chiral polymers containing quaternary ammonium groups can be prepared as reported in Scheme 6, by direct copolymerization of functional monomers with chiral ones (Refs. 71 and 76). The utilization of these systems as catalysts in reactions carried out under phase transfer conditions does not give rise to any appreciable loss of the stereochemical requirements of the polymers, indicating the maintenance of the chiral environment of the catalytic sites. On the contrary, during recycle experiments the catalytic activity is progressively reduced, due to Hofmann-type degradation of the quaternary ammonium groups, thus preventing so far any large scale application.

Scheme 6 Polymeric onium salts by chemical transformation of preformed polymers:



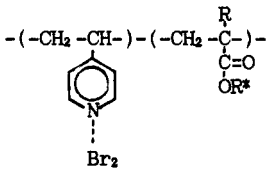
R = CH_3, C_2H_5 R' ◻ H, CH_3 R* = COOMenthyl* X = Br, I

To overcome this drawback, linear and crosslinked polymers containing polyglyme and crown ethers (**60-62**) have been synthesized (Refs. 71 and 76).

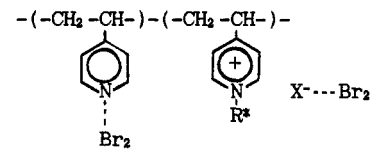


R* = Menthyl*

By following the above reported procedures, an analogous series of crosslinked chiral polymeric catalysts was prepared by suspension polymerization in the presence of a porogen. The catalytic activity of both linear and crosslinked polymers was tested in the alkylation and dichlorocarbenation of chiral and prochiral substrates, in the oxidation of racemic alcohols, and in the $NaBH_4$ reduction of prochiral ketones carried out under phase transfer conditions (Refs. 71-73). In all cases the investigated systems display a high catalytic activity, but no significant control on the reaction stereochemistry. This last observation is in accord with the results obtained in a CD study (Ref. 77) indicating that in the case of quaternary ammonium salts derived from (-)-ephedrine, an appreciable chirality of the reactive anion is observable only in tight ion-pairs. As a consequence it seems very likely that under the usual phase-transfer conditions the possible asymmetric induction arising from tight ion-pairs is hidden by the overwhelming reactivity of the non-chirally perturbed free anions. Analogously no asymmetric induction is observed in the dibromination of chiral and prochiral olefins by bromine adducts with linear and crosslinked chiral polymers containing pyridine nuclei (**63**), even if CD spectra of these complexes evidence some chiral perturbation of the polymer bound bromine (Refs. 78-80).



63 R = H, CH_3 R* = Menthyl*



64 R* = (S)-2-methylbutyl

FINAL REMARKS

In the present review paper effort has been provided to highlight the major results gained in the use of metal-free polymer catalysts characterized by the presence of catalytically active groups embodied in chiral environments as generated by local or long range asymmetric perturbation. A structure-activity relationship has been searched, with particular relevance to any cooperative effect in terms of anchimeric assistance by different functional group (multifunctional catalysis), hydrophilic-hydrophobic balance, and more in general by macromolecular structure, both of primary and second order type. The examination has been limited to chiral synthetic polymers specifically prepared for this purpose, that have been collected in two major sections. In the first section evidences have been analyzed of the activity in the cleavage of racemic and prevailing chiral activated esters by linear polymers loaded with imidazolyl or oxime group that display esterolytic activity in water-organic medium under homogeneous conditions. In the second section, that is by far less homogeneous in terms of the reaction type and nature of the substrates that have been taken into account, the polymer catalysts do operate mainly under heterogeneous conditions. The prochirality of the substrates that have been submitted to polymer catalyzed chemical transformation constitutes the only common feature to that section involving essentially oxidative, reductive and nucleophilic addition to carbon-carbon or carbon-oxygen double bonds. Despite the great deal of effort paid to the fascinating and challenging area of asymmetric reactions promoted by chiral polymer catalysts the information gained until now, eventhough do not appear of any outstanding value to practical exploitation in preparative organic chemistry, with the only exception of some Michael-type reaction they lend themselves to accrue elements valuable to mimick somehow the more elaborate mechanism of enzyme-catalysis and shine light on the relation structure-activity in catalytic processes discriminating on chiral grounds.

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